DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 12/3/09. Claim(s) 1-20, 22-23, 25, 27-29, 31-35 have been cancelled. Claim(s) 43-49 have been added. Claim(s) 21, 24, 26, 30, 36-49 are pending. Claim(s) 40 has been amended. Claim(s) 21, 24, 26, 30, 36-49 are examined herein.

Applicant's amendments have rendered the objection over claims 40-42 in the last Office Action moot, therefore hereby withdrawn. Accordingly, claim 30 is still objection to for reasons of record. Claims 40-49 are free of the prior art and now in condition for allowance.

Applicant's arguments with respect to the 103(a) rejection of the last Office Action has been fully considered but found not persuasive. The 103(a) rejection is maintained for reasons of record and repeated below for Applicant's convenience.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim(s) 21, 24, 26, 36-39 are rejected under 35 U.S.C. 103(a) as being obvious over Chamberlain et al. (US Patent Application 2005/0234083 A1) in view of Klaviniskis et al. (US Application 2003/014792 A1) and Ryan (US Patent 4,171,353).

The instant claims are directed to a composition comprising a SMIP compound of formula XXI and an antigen in an oil-in-water emulsion.

Chamberlain et al. teach benzimidazole derivatives for the treatment of hyperproliferative diseases (abstract). For example, an effective amount of a compound of formula I used to treat colon and breast cancers will be in the range of 0.1 to 100 mg/kg body weight per day (section 0413). A preferred compound is N^5, 1-Dimethyl-N^5-[2-({4-[(methylsulfonyl)methyl]phenyl}amino)pyrimidin-4-yl]- N^2-phenyl-1H-benzimidazole-2,5-diamine trifluoroacetic acid (Example 5, section 0755). Chamberlain et al. teaches that other therapeutic agents may be employed in combination with the disclosed compounds. In particular, in anti-cancer therapy, combination with other chemotherapeutic, hormonal, or antibody agents is envisaged (section 0414). Chamberlain et al. also discloses pharmaceutical oil-in-water emulsions (section 0394).

Examiner respectfully reminds Applicant that the term "vaccine" will be given little patentable weight since it is deemed preamble to the pharmaceutical composition claim.

It is respectfully pointed out that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish from each other. If the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Thus, the intended use of a composition claim will be given no patentable weight.

It is further respectfully pointed out that a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951). See MPEP 2111.02.

Examiner respectfully point out that the limitations in claim 21 regarding "amount effective to enhance the immune response in a subject to the antigen" and in claim 26 regarding "wherein the immune response is the cellular production of one or more cytokines" are inherent since a composition and its properties are inseparable, especially in the absence of a range of dosages of the active agent.

"Products of identical chemical composition can not have mutual exclusive properties." Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. The burden is shifted to the applicant to show that the prior art product does not inherently possess the same properties as the instantly claimed product.

It is well known in Patent Law that if applicants are claiming a biological pathway as the basis for their invention then a mechanism by which the active ingredient gives the pharmacological effect does not alter the fact that the compound has been previously used to obtain the same pharmacological effects which would result from the claimed method. The patient, condition to be treated, and the effect are the same. An explanation of why that effect occurs does not make novel or even unobvious the treatment of the conditions encompasses by the claims.

However, Chamberlain et al. fail to disclose specifically an antigen.

Klaviniskis et al. disclose a composition comprising spores of Bacillus subtilis as a method of stimulating immune responsiveness in a subject. The spores have an adjuvant, immunomodulatory, immune potentiation effect in a subject (abstract). Klaviniskis et al. also disclose that antigens can be used as adjuvant in the present composition (pg. 15, section 0155) to boost an immune response in a mammal (abstract). In addition to the MF59 adjuvant (pg. 2, section 0014), other antigens that

are mentioned to be useful are influenza, hemagglutinin, and neuraminidase (pg. 14, section 0147). Furthermore, Klaviniskis et al. disclose that the present composition can be used to treat colon and breast cancers (pg. 7, section 0082-0083).

Ryan teach that immunological adjuvants most commonly used to enhance immune responses in animals including man are generally divided into two types, one being oil-in-water emulsion type adjuvant. The oil-in-water emulsion type adjuvants provide a slow release of the antigen by virtue of its emulsified state in the oil (col. 1, lines 26-39).

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed invention was made, to combine the antigens as taught by Klaviniskis et al. with the oil-in-water emulsion composition as taught by Chamberlain et al.

A person of ordinary skill in the art would have been motivated to combine the antigens as taught by Klaviniskis et al. with the oil-in-water emulsion composition as taught by Chamberlain et al. because: (1) Chamberlain and Klaviniskis et al. are analogous art since both disclose a method of treating colon and breast cancers; (2) Chamberlain et al. teaches that other therapeutic agents may be employed in anti-cancer therapy; (3) Klaviniskis et al. disclose a composition comprising spores, which contain adjuvants that have an immunomodulatory effect and stimulates immune responsiveness; and (4) Chamberlain et al. discloses oil-in-water emulsion, which are well-known immunological adjuvants that provide slow release of the antigen. Therefore, one of ordinary skill in the art would have had a reasonable expectancy to

successfully make a composition comprising the active agent disclosed by Chamberlain et al. and the antigen and adjuvant disclosed by Klaviniskis, that would effectively treat colon and breast cancers by stimulating the immune system and enhancing an immune response, while providing slow release of the antigen.

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... The idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

Claim Objections

Claim 30 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Response to Arguments

At the outset, Applicant requests that the Examiner clearly identify the level of skill of the ordinary practitioner of the art so that the record can be made complete for appeal.

Examiner responds by stating that one of ordinary skill in the art could be at the level of a Master's degree in immunology. Certainly, more highly trained individuals, such as medical practitioners and PhDs also qualify.

Applicant argues that the Examiner has improperly disregarded express claim limitations in claims 21 and 26 regarding the "amount effective to enhance the immune response in a subject to the antigen" and "wherein the immune response is the cellular production of one or more cytokines."

Applicant is reminded that the claims are drawn to a composition and not methods of use. Therefore, the limitations in claims 21 and 26 do not change the scope of the instant invention. In fact, no amount range is claimed, thus any amount taught by the prior art is sufficient to meet this limitation. Should Applicant disagree, Examiner strongly encourages the Applicant to show factual evidence that the composition taught by the cited prior art does not "enhance the immune response in a subject to the antigen" and "wherein the immune response is the cellular production of one or more cytokines." Since the same composition is taught by the prior art, there cannot be a situation where this mechanism of action occurs in vivo in the claimed invention and not in the cited prior art. This is because all components of the claimed composition has been taught by the cited prior art.

Applicant argues that the Chamberlain reference does not disclose any teachings that the benzimidazole compounds can serve as an adjuvant in a composition or induce an immune response. Accordingly, not only does the reference fail to disclose an antigen in combination with these compounds, it also offers no reason to combine its compounds with an antigen or to use them in any vaccine-like composition.

In response, Examiner would like to remind Applicant that the claims are drawn to a composition, therefore the term "vaccine" will be given little patentable weight since

it is considered preamble or intended use for the composition. Accordingly, since the claims are drawn to a composition, a teaching of the active agent in a composition is sufficient, no matter what the active agent is called or what purpose it was intended for. Therefore, the fact that Chamberlain may or may not refer to its compounds as adjuvants or antigens is irrelevant in the context of the obviousness rejection. What is relevant is that Chamberlain teaches these compounds for the treatment of hyperproliferative diseases, such as colon and breast cancers, which also can be formulated as oil-in-water emulsions.

"The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant." >See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc., 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings.");< *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904 (1991) See MPEP 2144.

Applicant argues that Klaviniskis does not disclose or suggest that an 'antigen' acts as an adjuvant, only that the Bacillus spores as an adjuvant can be used along with

an antigen. Thus it provides no reason to combine the spores from Klaviniskis (which are described as adjuvants, and have no disclosed therapeutic activity at all in the absence of an added antigen) with the compounds of Chamberlain, which are indicated to be therapeutic but not antigenic.

This is not persuasive because Klaviniskis clearly teaches the use of Bacillus spores as an adjuvant in combination with an antigen. Klaviniskis also teach that antigens can be used as an adjuvant in the present composition (pg. 15, section 0155). Some disclosed antigens to be used in the Klaviniskis reference are influenza, hemagglutinin, and neuraminidase (pg. 14, section 0147). It is also noted that the instant claims use the open transitional language, comprising, so as to not preclude the use of antigens.

Applicants argue that there is no motivation to combine Chamberlain with vaccine-related compositions of any sort. Specifically, Chamberlain does not contemplate any of its 'therapeutic agents' in an immunological composition eliciting an immune response. Applicants argue that it is well known in the art that a vaccine composition is not generally combined with therapeutic agents. Applicants argue against the Kerkhoven case law by stating that therapeutic treatment and vaccination/immune response development are just not the same purpose.

This is not persuasive because Applicant's view of the state of the art is incorrect. In fact, there are currently many research strategies involving therapeutically administering cancer vaccines to subjects with tumors. In this manner, cancer vaccines can be considered as therapeutic agents. Accordingly, these vaccines can be

combined with other therapeutic agents for the same purpose of treating cancer. This is corroborated by the fact that Klaviniskis discloses that the spores can be used in a method wherein the spores are administered with cancer vaccine components and in combination with an anti-cancer agent, as admitted by the Applicant on the bottom of page 9 of the response.

Examiner reminds Applicant that the standard for obviousness is not absolute but rather a reasonable expectation of success. Combining two compositions for the same purpose of treating cancer does not need to focus on such minor details such as toxicities, tolerability, efficacy, and bioavailability. These details are the burden placed on the Applicant to show that such combination does not have a reasonable expectation of success. In the present case, there is no factual evidence regarding the toxicities, tolerability, efficacy, and bioavailability of the combination provided by the cited prior art.

The Valiante Declaration under 37 CFR 1.132 filed 5/4/09 is insufficient to overcome the rejection of claims 21, 24, 26, 36-39 based upon Chamberlain et al. (US Patent Application 2005/0234083 A1) in view of Klaviniskis et al. (US Application 2003/014792 A1) and Ryan (US Patent 4,171,353) as set forth in the last Office action. The Declaration states that it is well known in the art that vaccine compositions require specialized formulations and are not ordinarily combined with small molecule therapeutic agents. In addition, one of skill in the art would recognize that oil-in-water formulations of small molecule drugs are not necessarily suitable for use as vaccine formulations. Thus, the skilled artisan would not have inferred that the oral oil-in-water emulsions by Chamberlain et al. would be useful as vaccine adjuvants.

This is not persuasive because the arguments presented in the Valiante Declaration are essentially the same ones presented throughout prosecution. Examiner notes that no factual evidence has been presented nor does the Valiante Declaration show evidence of the state of the prior art. In the absence of these types of evidence, response to the arguments is deferred to the above discussion regarding obviousness.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Applicant argues nonobviousness on dependant claim 39, which recites a second adjuvant as an oil-in-water emulsion. Applicants also argue that Chamberlain only discloses oral oil-in-water emulsions and not the claimed oil-in-water adjuvant. Although Chamberlain discloses oral oil-in-water emulsions, they are not necessarily disclosed as an 'adjuvant,' therefore should be considered nonobvious as they must be used as a carrier instead. Furthermore, the Ryan reference only discloses the advantages of an oil-in-water emulsion formulated as an injection, therefore teaching away from oral administration. Applicants then go in great detail about how the tumor antigens (polypeptides) of Klaviniskis cannot be formulated for oral administration as taught by Chamberlain because of various mechanistic reasons.

At the outset, it is not understood why the Applicant is arguing so much about such a minor detail of the instant invention. Is Applicant proposing that the oil-in-water emulsion limitation is the novelty of the instant invention? Nonetheless, in response, Examiner finds Applicant's arguments not persuasive for the reasons below. Firstly, Chamberlain does not limit its formulations for oral administration. In fact, Chamberlain

clearly teaches that its pharmaceutical formulations may be adapted for administration by any appropriate route, for example, oral, rectal, nasal, topical, vaginal, intraveneous, or intradermal routes. Such formulations may be prepared by any method known in the art of pharmacy (pg. 14, left column, paragraph 0393). Therefore, Applicant's basis for arguing is overcome since Chamberlain is not limited to only oral administration. Furthermore, Ryan clearly shows the advantages of formulating oil-in-water emulsion type adjuvants, for example to provide a slow release of the antigen by virtue of its emulsified state in oil.

Applicant argues that just because two drugs could both be used in methods to treat a common disorder, it does not provide a motivation to combine the two into a single composition, in view of the expected differences in dosages, frequency, timing, route of administration, dietary effects, drug toxicities, tolerability, efficacy, and bioavailabilty.

This is not persuasive because the obviousness rejection has made a prima facie case of obviousness. It is Applicant's burden to show that there would be no motivation to combine of the two drugs, in view of the potential issues and side effects. Examiner requests factual evidence to this effect and not merely opinions and conjectures.

Regarding the establishment of unexpected results, a few notable principles are well settled. It is applicant's burden to explain any proffered data and establish how any results therein should be taken to be unexpected and significant. See MPEP 716.02 (b). The claims must be commensurate in scope with any evidence of unexpected results. See MPEP 716.02 (d). Further, a DECLARATION UNDER 37 CFR 1.132 must

compare the claimed subject matter with the closest prior art in order to be effective to rebut a prima facie case of obviousness. See MPEP 716.02 (e). Applicants fail to provide clear and convincing evidence to support the alleged unexpected benefit.

For the record, Applicant claims unexpected results but have not provided any factual evidence showing unexpected results or an explanation why such results are unexpected.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

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/Yong S. Chong/
Primary Examiner, Art Unit 1627

YSC